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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference F16536 CPF	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB 02/01554	International filing date (day/month/year) 08.05.2002	Priority date (day/month/year) 12.04.2002
International Patent Classification (IPC) or both national classification and IPC C07C51/41		
Applicant TECHNICAL AND COMMERCIAL SERVICES INTERNATIONAL ..		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 4 sheets, including this cover sheet.
  - ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

- This report contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  18.09.2003	Date of completion of this report  19.11.04
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Bedel, C  Telephone No. +49 89 2399-2506 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/IB 02/01554**

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

2-28 as originally filed  
1, 1a filed with telefax on 19.04.2004

**Claims, Numbers**

1-18 filed with telefax on 19.04.2004

**Drawings, Sheets**

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/B 02/01554**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims	1-18
	No: Claims	
Inventive step (IS)	Yes: Claims	1-18
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	

- 2. Citations and explanations**  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/IB 02/01554

The present set of claims has been amended so as to include the reaction time in the first reactor. This is supported by the subject-matter of claim 2 as filed.

The following documents are referred to :

D1: US-A-4335257

D2: US-A-2396115

D3: WO-A-0232235

D4: US-A-470000

The present application concerns a process for making acid salts, which differs from the processes of the documents D1-D4 by the fact that the reaction slurry is transferred into a second reaction vessel and by the fact that the reaction time in the first reactor is controlled so as to stay within 3 and 180 seconds.

The inventiveness of the present application can rely on the fact that it is not obvious to design a 2 pot process for making carboxylic acid salt, while adjusting the reaction time within both reactors so as to have a maximum amount of water in the reaction mixture. The advantages obtained by this process (see page 28) are unexpected by the skilled person.

Further remarks :

In order to comply with the requirements of rule 5.1.ii PCT, the most relevant prior art should be cited and briefly discussed.

Rec'd PCT/PTC 12 OCT 2000/511004  
Empf.zeit: 19/04/2004 10:08  
Empf. nr.: 156 P.013A METHOD OF MAKING SALT

THIS INVENTION relates to a method of making a salt.

The metal salts of lower molecular mass acids such as substituted and unsubstituted  $C_1 - C_{10}$  acids, aromatic carboxylic acids of the formula  $Ph-(CH_2)_x-CO_2H$  where  $x$  is 0 - 4, benzoic acid and phenylacetic acid are typically made by reacting the acid with a basic salt of the metal such as its hydroxide or carbonate. In some cases, the reactions are conducted in a relatively dilute aqueous medium and isolation of the salt of the acid requires removal of excess water and a drying step. In other cases, the acid is added to a slurry of a base such as calcium carbonate or calcium hydroxide in a closed vessel. The slurry then progressively thickens and passes through a "plastic" stage after which it is dried. Handling the product after the plastic stage is generally difficult. Furthermore large scale production process drying is energy intensive and expensive. It is an object of the invention to address these problems.

A related process for the preparation of the calcium salt of 2-hydroxy-4-thiomethylbutyric acid is described in PCT/IB01/02087.

According to a first aspect of the invention, there is provided a method of making the salt of an acid selected from  $C_1 - C_{10}$  carboxylic acids, aromatic carboxylic acids of the formula  $Ph-(CH_2)_x-CO_2H$  where  $x$  is 0 - 4, and glycerophosphoric acid, the method including the steps of

combining and mixing the acid and a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium, or a mixture of any two or more thereof, in a first reaction zone, the combining and mixing step being carried out over a first period to produce a reaction mixture in the first reaction zone;

Empf.nr.: 156 P.014

Empf.zeit: 19/04/2004 10:08

transferring the reaction mixture at the end of the first period from the first  
reaction zone to a second reaction zone the transferring step being carried out over  
5 a second period; and

allowing heat generated by reaction between the acid and the base in the

Empf.nr.: 156 P.007

Empf.zeit: 19/04/2004 10:06

1. A method of making the salt of an acid selected from  $C_1 - C_{10}$  carboxylic acids, aromatic carboxylic acids of the formula  $Ph-(CH_2)_x-CO_2H$  where  $x$  is 0 - 4, and glycerophosphoric acid, the method including the steps of

combining and mixing the acid and a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium, or a mixture of any two or more thereof, in a first reaction zone, the combining and mixing step being carried out over a first period of 3 - 180 seconds to produce a reaction mixture in the first reaction zone;

transferring the reaction mixture at the end of the first period from the first reaction zone to a second reaction zone the transferring step being carried out over a second period; and

allowing heat generated by reaction between the acid and the base in the second reaction zone to drive off sufficient water to produce a product mixture containing less than about 8% (m/m) water, provided that the acid is not 2-hydroxy-4-thiomethylbutyric acid.

2. A method as claimed in Claim 1, in which the second period is 2 - 60 seconds.

3. A method as claimed in Claim 1, in which the combining step takes about 2 - 60 seconds.

4. A method as claimed in Claim 2, in which the first period is 3 - 60 seconds.

5. A method as claimed in any one of Claims 2 to 4 inclusive, in which the second period is 3 - 30 seconds.

6. A method as claimed in any one of the preceding claims, in which the carboxylic acid is a substituted or an unsubstituted  $C_1 - C_{10}$  acid.

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Empf.zeit: 19/04/2004 10:06

7. A method as claimed in any one of Claims 1 to 6 inclusive, in which carboxylic acid is monocarboxylic acid selected from formic acid, acetic acid, propanoic acid, butanoic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid and their alkylated or hydroxylated analogues.

8. A method as claimed in any one of Claims 1 to 6 inclusive, in which the carboxylic acid is a dicarboxylic acid selected from oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sibaccic acid and their unsaturated, alkylated or hydroxylated analogues.

9. A method as claimed in any one of Claims 1 to 5 inclusive, in which the acid is benzoic acid or phenylacetic acid.

10. A method as claimed in any one of the preceding claims, in which the acid is in the form of an aqueous solution.

11. A method as claimed in Claim 10, in which the aqueous solution has a concentration of about 60 - 99,5 % by mass of the acid.

12. A method as claimed in any one of the preceding claims, which includes allowing the heat generated to drive off sufficient water to produce a product mixture containing less than about 2,5 % water.

13. A method as claimed in any one of Claims 10 to 12 inclusive, which includes the prior step of warming the solution of acid to 50 - 96 °C.

14. A method as claimed in any one of the preceding claims, which includes the further steps of successively combining and mixing a plurality of batches of the acid and base with water in the first reaction zone to produce successive batches of the reaction mixture and successively transferring each of the batches to the same second reaction zone.



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Empf.zeit: 19/04/2004 10:07

15. A method as claimed in any one of the preceding claims which includes agitating the reaction mixture in the second reaction zone.

5. 16. A method of making salt of an acid selected from  $C_1 - C_{10}$  carboxylic acids, aromatic carboxylic acids of the formula  $Ph-(CH_2)_x-CO_2H$  where  $x$  is 0 - 4, benzoic acid, and glycerophosphoric acid, the method including the steps of

combining and mixing the acid, a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium, or a mixture of any two or more thereof and water in a first reaction zone to produce a reaction mixture in the first reaction zone;

continuously transferring the reaction mixture from the first reaction zone to a second reaction zone, the reactants being added to the first reaction zone in successive batches and the reaction mixture being continuously removed from the first reaction zone at a rate which is selected so that the residence time of the reaction mixture in the first reaction zone is between about 1 and 180 seconds; and

allowing heat generated by reaction between the acid and the base in the second reaction zone to drive off sufficient water to produce a product mixture containing less than about 8% water, provided that the acid is not 2-hydroxy-4-thiomethylbutyric acid.

17. A method as claimed in Claim 16 which the heat generated is allowed to drive off sufficient water to produce a product mixture containing less than about 2,5% water.

18. A continuous method of making a salt of an acid selected from  $C_1 - C_{10}$  carboxylic acids, aromatic carboxylic acids of the formula  $Ph-(CH_2)_x-CO_2H$  where  $x$  is 0 - 4, and glycerophosphoric acid, the method including the steps of

simultaneously feeding, into a reaction zone, an aqueous solution of the acid, and a base selected from the oxides, hydroxides and carbonates of sodium, potassium, calcium and magnesium or a mixture of any two or more thereof to produce a reaction mixture in the reaction zone; and

Empf.zeit: 19/04/2004 10:07

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a rate which is selected so that the residence time of the reaction mixture in the reaction zone is 3 – 180 seconds and is sufficient to initiate reaction between the acid and the base but not sufficient to drive off water from the reaction mixture and allowing heat generated by further reaction between the acid and the base in the second zone to drive off sufficient water to produce a product mixture containing less than about 8% water, provided that the acid is not 2-hydroxy-4-thiomethylbutyric acid.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 02/01554

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C51/41 C07F9/09 C07C53/122 C07C53/10 C07C59/265

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 335 257 A (CUMMINS EARL W ET AL) 15 June 1982 (1982-06-15) column 3; claims; example 1 ---	1, 18, 20
Y	US 2 396 115 A (NICHOLLS RICHARD S) 5 March 1946 (1946-03-05) claims; example 1 ---	1, 18, 20
X	---	21-23
X, P	WO 02 32235 A (NIELSEN KIM R ;NUTRAPURE INC (US); HAGER DENNIS M (US); STERN WILL) 25 April 2002 (2002-04-25) claims; examples ---	1, 18, 20
A	US 4 700 000 A (MERKEL DIETER ET AL) 13 October 1987 (1987-10-13) claims; examples -----	1, 18, 20
X	-----	21, 23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*A\* document member of the same patent family

Date of the actual completion of the international search

10 December 2002

Date of mailing of the international search report

19/12/2002

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/01554

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4335257	A	15-06-1982	AR 225363 A1	15-03-1982
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			SU 1091854 A3	07-05-1984
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			WO 0232235 A2	25-04-2002
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US 4700000	A	13-10-1987	DE 3215752 A1	03-11-1983
			DE 3360027 D1	24-01-1985
			EP 0093317 A1	09-11-1983
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